

## **REMARKS**

### **Preliminary Remarks**

Applicants gratefully acknowledge the courtesy shown by the examiner at the interview on April 20, 2004, attended by inventor Randolph Noelle and the undersigned.

Claims 1, 4, 7-11, 13-15, 17, 20-21, 24-26, 28-31, 34-35, 38-43 and 46-50 are currently pending in this application.

Independent claims 1, 15, 30, and 42 are amended to specify that the disclosed method is one that induces T cell non-responsiveness to a donor antigen, or to a donor cell, tissue or organ that expresses at least one such antigen, support for which is found in the specification; for example, on page 5, lines 16-27, which states that T cells that are induced to have tolerance to a donor antigen do not show an immune response to a donor cell tissue or organ that expresses the antigen.

Claims 1, 15, 30 and 42 are further amended to specify that the disclosed T-cell non-responsiveness is induced in a human recipient or subject. Support for this amendment is found in the specification; for example, on page 4, lines 35-36, which states that the term "recipient" refers to a subject into whom a tissue or organ graft is to be transplanted. Furthermore, on page 10, lines 32-34 reads that the term subject is intended to include living organisms in which an immune response can be elicited, e.g., mammals. Examples of subjects include humans, dogs, cats, mice, rats and transgenic species thereof.

Claims 1, 15, 30 and 42 are further amended to specify that the method for inducing T-cell non-responsiveness comprises administering anti-human gp39 antibody. Support for the anti-human gp39 antibody can be found at original claim 5.

Claim 1, 15 and 42 are further amended to recite that the method for inducing T cell non-responsiveness comprises administering the recipient a donor cell and an anti-human gp39 antibody prior to transplantation of the tissue or organ. Support for this can be found at original claims 12, 27 and 42.

Claims 1, 15 and 42 are further amended to disclose a method for inducing T cell non-responsiveness to an allogeneic or xenogeneic or just allogeneic (in claim 42) donor tissue or organ comprising administering to the recipient a donor cell. Support for the allogeneic or xenogeneic {W:\20052\1200520us4\00227430.DOC [REDACTED]}

donor tissue or organ can be found in the specification, for example, at page 9, lines 31-34. Support for a donor cell can be found in the specification, for example, at page 5, lines 4-9.

No new matter has been introduced by these amendments. Therefore, entry and consideration of the amendments are respectfully requested.

## Patentability Remarks

**35 U.S.C. § 112, First Paragraph (Enablement)**

Claims 1, 4-15, and 17-50 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described in the specification in a manner so as to enable one skilled in the art to use the claimed invention, for the reasons of record stated in the Final Office Action. Specifically, the Examiner contends that the specification does not enable one skilled in the art to use a gp39 antagonist in combination with an antigen-presenting cell to induce T cell tolerance to the antigen in a live subject.

The claims are amended by replacing the term “tolerance” with “non-responsiveness”. The specification teaches that T cell tolerance to a donor antigen on a donor cell, tissue or organ is induced by binding of an antibody that blocks the interaction of gp39 on the surface of a T cell and a gp39 receptor on the surface of a donor antigen-presenting cell that mediates the response of the T cell to the antigen. The specification states that T cells that are non-responsive to a donor antigen do not show an immune response to a donor cell tissue or organ that expresses the antigen (e.g., see pages 5 and 10 of the specification). As disclosed in the specification (e.g., Example 1), the period of T cell tolerance or non-responsiveness that is induced by the disclosed method is of sufficient duration to confer therapeutic benefit by inhibiting the rejection and prolonging the survival of the transplanted cells, tissue, or organ in the transplant recipient. The Applicants respectfully submit that from the description of the disclosed invention in the specification, a person skilled in the art would understand that “induction of T cell tolerance to antigen” as used in the claims and specification is, in effect, induction of T cell non-responsiveness to the antigen.

The attached commentary by Herman Waldmann (Waldmann, Nature Medicine 2003, 9:1259-1260; Exhibit A) reports on studies that show that anti-CD40L (*i.e.*, anti-gp39) antibodies destroy activated T-cells, which would indeed render the cells unresponsive. (Waldmann, p. 1259,

col. 1). This unresponsiveness manifests itself as tolerization to allo- or xeno-antigens. (Waldmann, p. 1260, col. 2).

In light of the present amendment, the disclosure in the specification, and Waldmann, the claims as amended are enabled. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

**35 U.S.C. § 103(a) (Obviousness)**

Claims 1, 4, 5, 7-15, 17, 18, 20-32, 34-44, and 46-50 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,403,091 to Lederman et al. (“Lederman”) in view of U.S. Patent No. 5,597,563 to Beschorner et al. (“Beschorner”) and U.S. Patent No. 6,056,956 to Cobbold et al. (“Cobbold”) (collectively the “tolerization references”), for the reasons stated in the Final Office Action.

Applicants' respectfully traverse this rejection, for the reason that no combination of the cited references would have given the skilled artisan any incentive to induce T cell non-responsiveness to an allogeneic or xenogeneic donor tissue or organ in a human recipient comprising administering (a) a donor cell and (b) an anti-human gp39 antibody, or human soluble CD40 molecule, much less any reasonable expectation of doing so. Lederman describes antibodies to an uncharacterized antigen (5c8) present on activated but not resting T-cells, which antibody inhibited T-cell activation of B-cells. The other two references describe unresponsive treatment methods which suggest nothing about or actually teach away from any involvement of gp39/CD40 interactions.

As discussed during the interview, the mechanism of tolerance achieved using the non-depleting anti-CD4 and anti-CD8 antibodies of Cobbold would provide no motivation to substitute an anti-gp39 antibody to achieve tolerization. Moreover, as demonstrated by Cobbold, non-depleting antibodies, by their very name, teach away from the use of antibodies that induce T-cell non-responsiveness by ablation, *e.g.*, such as the anti-gp39 antibodies of the claimed invention. As discussed below, Berschorner directs one away from using any such antibodies.

Since Lederman only describes inhibiting B-cell responses by binding to the 5c8 antigen and the remaining references cannot be applied to the use of anti-gp39 antibodies, there is no motivation to combine references from the different groups.

### **Tolerization References:**

Contrary to the Examiner's interpretation of the Berschorner and Cobbold references, careful review of each reference, considering what it fairly teaches as a whole, reveals that:

***Anti-gp39 antibody would have deleterious affects on Berschorner's tolerization process.*** Beschorner teaches that antigen-specificity of immune tolerance is determined by the presentation of antigens by antigen-presenting cells (APCs) such as dendritic cells; see col. 1, lines 36-37), and describes a method for inducing antigen-specific immune tolerance that comprises (a) administering an immunosuppressive agent such as cyclosporin A that depletes recipient's thymic medulla of APCs, and then (b) infusing new APCs into the subject that contain the antigen to which tolerance is desired (see col. 2, lines 32-40; col. 5, lines 13-17; and col. 8, lines 1-4).

In Berschorner's tolerization process, the timing of the immunosuppressive treatment and APC recruitment or infusion is critical (Berschorner, col. 5, ll. 13-20, emphasis added):

The agent should be administered for a period of time long enough to deplete the thymic medulla of those APCs, such as dendritic cells, which are present at the beginning of therapy and is preferably withdrawn before the thymic medulla is repopulated with new APCs which induce tolerance for the antigen. By withdrawing the immunosuppressive agent at this time, deleterious effects of the agent on the new APCs are minimized.

Hence, to avoid deleterious effects, Berschorner teaches that the immunosuppressant should not be present when the new APCs start presenting their antigen or autoantigen to T-cells, which leads to subsequent T-cell activation and gp39 presentation. Accordingly, an anti-gp39 antibody (which the Examiner refers to as having alleged immunosuppressive properties) would have no effect prior to administration of the desired APCs to induce tolerance, *i.e.*, if used as an immunosuppressant according to Berschorner, as no relevant gp39 expressing T-cells are present prior to administration of APCs. Again, following Berschorner's teaching, anti-gp39 antibodies would be present in reduced amounts, if at all, when T-cell activation (expression of gp39) in {W:\20052\1200520us4\00227430.DOC \[REDACTED\]}

responsive to the APCs occurs. Once gp39 is expressed (after administration of APCs), there is no longer any anti-gp39 antibody present. Moreover, anti-gp39 antibodies would have a deleterious effect on the APCs since they block gp39 binding to CD40, the very thing Berschner warns against. Berschner is anathema to the present invention. Such clear incompatibility, such teaching away by a reference, precludes a determination of obviousness.

***Cobbold's teachings are irrelevant to anti-gp39 antibodies.*** Cobbold describes the use of non-depleting anti-CD4 and anti-CD8 antibodies in eliciting tolerance to an antigen. Antibodies against these targets have long been known to have a direct effect on T-cell viability and to induce immunosuppression (see, e.g., Cobbold, col. 1, ll. 24-45). These teachings cannot, however, be randomly extrapolated to antibodies against any T-cell antigen, particularly to antibodies against gp39 which were believed to only inhibit the T-cell's activation of a B-cell. To the extent that Lederman is relevant, it only shows the ability of an antibody to an otherwise uncharacterized T-cell antigens, 5c8, to inhibit T-cell activation of B-cells. Lederman also shows, using an anti-CD4 antibody control, that the antibodies are very different, further precluding the combination asserted by the examiner (see Lederman Example 7 at col. 23, line 48-col. 24, line 53).

The ability of an anti-gp39 antibody to induce T-cell non-responsiveness was a novel finding, first disclosed in the present application, and not in any way suggested by Cobbold or any other reference cited by the Examiner.

As discussed at the interview, Cobbold's teaching of depleting antibodies to CD4 and CD8 to induce tolerance would in no way provide a suggestion or motivation to substitute anti-gp39 antibodies, if any references of record in fact suggested such antibodies, for the non-depleting anti-CD4 and anti-CD8 antibodies. Cobbold describes development of a regulatory T-cell population (elicited through the non-depleting antibodies), as shown in Table 5 (Cobbold, col. 19, lines 23-43). The data in Table 5 show that transfer of normal spleen cells could not break the tolerant state unless recipient CD4+ T-cells were depleted first; "the immune system of tolerant animals does not allow normal virgin T-cells to express their immune potential" (Cobbold, col. 13, lines 4-12).

Nothing in Cobbold supports a reasonable expectation that anti-gp39 antibodies could possibly achieve the results of non-depleting anti-CD4 antibodies. Indeed, the mechanisms of action {W:\20052\1200520us4\00227430.DOC {REDACTED} }

of antibodies targeted to these different antigens could not be more different. For example, Waldmann points out that anti-CD40L antibody therapy operates by destruction of activated T-cells, not by costimulation blockade. (Waldmann, p. 1259, col. 1).

Furthermore, assuming that an antibody to any T-cell antigen will have the same effect on the T-cell is unreasonable CD4 (and CD8) are constitutive antigens. Depleting antibodies effectively remove all T-cells. Cobbold's discovery of the effects of non-depleting antibodies; which appear to elicit a regulatory T-cell population, defied conventional wisdom (*see* Waldmann, Immunol. Rev. 2002-185:227-235, hereinafter Waldmann II, at p. 231, col. 1: "In the early 1990s, mention of the word *suppression* at a scientific meeting would inevitably provoke disbelief or concern for my health"). There is no objective reason to suppose that an antibody to a different T-cell antigen would elicit the same sort of result. Thus, the reference fails to supply the motivation for the combination, and absolutely fails to provide any reasonable expectation of successfully employing a different anti-T-cell antigen antibody.

The dissimilarities between CD4 and gp39 further distinguish the present invention: CD4 is a constitutive T-cell molecular, while gp39 is only transiently expressed on activated T-cells; CD4 mediates co-stimulatory signals in T-cells, while gp39 signals through CD40 on antigen presenting cells. These facts rebut any attempt to use Cobbold to somehow arrive at the claimed invention.

**Lederman:**

The Lederman patent, which corresponds to Patent No. 5,474,771 issued on December 12, 1995 (Lederman, col. 1, lines 6-8), describes administering antibody 5c8 to a subject to prevent the activation of B cells by T cells, in order to inhibit undesired humoral immune responses in the subject. Lederman states (col. 2, lines 15-19) (emphasis added):

This invention provides a monoclonal antibody which specifically recognizes and forms a complex with T-B cell activating molecule (T-BAM) (*now also known as CD40 ligand*) a protein located on the surface of activated T cells and thereby inhibits T cell activation of B cells.

However, the language of the specification (now also known as CD40 ligand) indicates that Lederman's realization in the published application that the 5c8 antigen corresponds to CD40 ligand, *i.e.*, gp39, was made public when the patent issued, not when the application was filed, which issue date is after the priority date of the present application, April 25, 1994. Other than this passing reference, there is no way to ascertain what T-cell molecule 5c8 represents, much less that it interacts with CD40 on B-cells. Thus, Lederman cannot suggest using an anti-gp39 antibody, *i.e.*, an antibody that blocks the interaction of gp39 and CD40, as claimed.

### **No Motivation to Combine**

Without any teaching or suggestion that anti-gp39 antibodies also might affect T-cell non-responsiveness, there would be no motivation to combine Lederman, which teaches an antibody that blocks T-cell activation of B-cells, with the “tolerization” protocols described by Berschorner, and Cobbold (“tolerization references”) in a method to induce T-cell non-responsiveness. Basic knowledge of the expression patterns of gp39 would certainly discourage the skilled artisan to use an anti-gp39 antibody in Berschorner’s protocol. The Examiner vaguely connects the “immunosuppressive regimens” used in the tolerization references to the “antagonists of the immune response” provided by the antibody references (office action, p. 6, 1<sup>st</sup> paragraph); however, “[t]he showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (emphasis added).

In this context, it is noted that the “antagonists of the immune response” provided by Lederman is only described as affecting B-cell activation. Based on the teaching of Lederman, the skilled artisan would not have believed that the “immunosuppressive regimens” described in the tolerization references could be achieved by an anti-gp39 antibody or even by Lederman’s antibody to the otherwise uncharacterized . Accordingly, there is no clear and particular motivation to combine the references as suggested by the Examiner.

### **No Reasonable Expectation of Success**

Even if combined, there would still be no reasonable expectation of success that the combined teachings of Lederman combined with the tolerization references would somehow lead to

a induction of T-cell non-responsiveness, because extrapolating one biological phenomenon to another, *e.g.*, that anti-gp39 antibodies would lead to a reduction in T-cell responsiveness simply because anti-CD4 antibodies do, or simply because they affect B-cell activation, could only be achieved using hindsight reconstruction based on the present disclosure.

For the reasons discussed above, the applicants submit that the present claims satisfy the requirements of 35 U.S.C. § 103(a), and request that the rejection of claims under § 103(a) be withdrawn.

The Examiner argues that by attacking the references separately, applicants somehow fail to rebut *prima facie* obviousness. However, as discussed above, the individual teachings of the references preclude combining their teachings, and even if combined, the references do not suggest the claimed invention, much less provide a reasonable expectation of success in achieving the invention.

It is further noted that the Examiner fails to explain how Lederman, which the Examiner notes teaches inhibition of B-cell activation to suppress immune response (Office Action, p. 5, ¶3) in any way suggests targeting T-cells for immunosuppression, as argued in this part of the office action (*Ibid*, ¶2).

Finally, the Examiner asserts that one of skill in the art would combine the teachings of the references, apparently without regard to timing issues (which disqualifies Berschner), or compatibility issues (which distinguishes Cobbold from Lederman). There must be some motivation to combine the references – other than the application's specification – but there is no objective basis in the references themselves to make such a combination.

**Judicially created doctrine of obviousness-type double patenting**

Claims 1-21, 24-35 and 38-50 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

claims 1-34 of U.S. Patent No. 5,683,693,

claims 1-34 of U.S. Patent No. 5,902,585, and

claims 1-7 of U.S. Patent No. 6,375,950.



A terminal disclaimer disclaiming patent term with respect to the terms of the cited patents will be submitted upon clarification of the inventorship, and thus ownership, as discussed below.

**Identification of inventors of the conflicting subject matter**

Paragraph 15 of the office action (p. 7) raises the issue of the differences in inventorship of the present application and U.S. Patent No. 6,375,950; and of U.S. Patent Nos. 5,683,693 and 5,902,585. As discussed previously with the Examiner, this has generated a need to investigate inventorship in the pending application. At the present time the investigation is ongoing. Inventorship will be corrected in the appropriate application or patent in due course.

**Conclusion**

Applicants respectfully request entry of the foregoing amendments and remarks in the prosecution of this application. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Dated:

Respectfully submitted,

By Stephanne Amoroso 51,401  
for

Paul F. Fehlner, Ph.D.  
Reg. No. 31,135  
Applicant's Attorney  
DARBY & DARBY P.C.  
P.O. Box 5257  
New York, New York 10150-5257  
(212) 527-7700  
(212) 753-6237 (Fax)

specific molecular factors that regulate hair-cell development, and to seek out the factors that trigger stem cells to develop as hair cells in the adult inner ear.

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## The new immunosuppression: just kill the T cell

Herman Waldmann

**Antibodies to the CD40 ligand have modulated the immune system in animal experiments and in human clinical trials. Assumptions about how these antibodies work are now reexamined (pages 1275–1280).**

It is now 50 years since Medawar demonstrated that immunological tolerance could be acquired in newborn mice<sup>1</sup>. Since then, the challenge to immunologists has been to achieve therapeutic tolerance in the areas of transplantation, autoimmune disease and allergy. The development of monoclonal antibodies to molecules crucial for T-cell activation has catalyzed attempts to achieve this goal. One such molecule is the CD40L, which engages CD40 on dendritic and B cells of the immune system, enabling T cells to become activated as a result.

Experiments showing that short courses of CD40L antibody therapy could achieve long-term graft survival in mice and primates have evoked enormous interest<sup>2,3</sup>. The primate studies predicted clinical utility and the outcome, interpreted as an effect of costimulation blockade, seemed perfectly consistent with a long-standing two-signal model for T-cell activation. However, the notion that antibodies to CD40L block, rather than destroy, target cells has been an unproven assumption.

In this issue, Monk *et al.*<sup>4</sup> rigorously examine this assumption and come to an unexpected conclusion. They show that much of the efficacy of anti-CD40L therapy derives not from costimulation blockade, but from destruction of activated T cells. The outcome is a selective purging of potentially aggressive T cells that have experienced antigen. These findings call for a reevaluation of numerous experiments

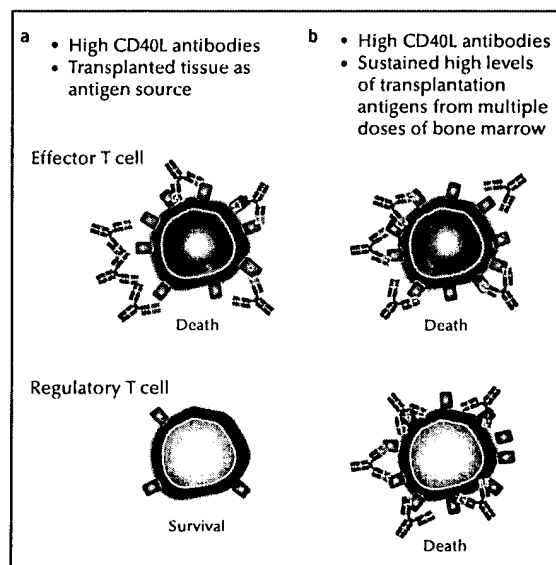
interpreted as consequential to costimulation blockade, and should affect future strategies for clinical use of antibodies to CD40L.

Rodent studies using coreceptor blockade with monoclonal antibodies to CD4 and CD8 were the first to show that tolerance to transplanted tissues could be acquired in adult mice<sup>5</sup>. CD4 and CD8 are constitutively expressed on T cells, so the claim of blockade rather than cell lysis has been undisputed because no loss of T cells could be observed. CD40L is not constitutively expressed on T cells, but is induced only after activation by the antigen receptor.

Consequently, visualization of T-cell killing has been difficult and has never been properly studied.

To examine this question, Monk *et al.*<sup>4</sup> transplanted skin to recipients mismatched across the whole major histocompatibility complex. They used a synergistic combination of a short course of antibody to CD40L and a 2-week course of the immunosuppressant rapamycin to obtain long-term graft survival. This therapy abolished the generation of graft-reactive cells expressing the cytokine interferon- $\gamma$ . Staining of draining lymph nodes from treated mice revealed deposition of complement protein C3 frag-

**Figure 1** CD40L and tolerance: proposed mechanism by which CD40L antibody therapy induces dominant tolerance when associated with transplanted tissue grafts, and deletional tolerance when combined with substantial infusions of donor bone marrow cells. (a) The transplanted skin provides alloantigens that drive many antigen-specific T cells to proliferate. Activated T cells become susceptible to the ablative effects of CD40L antibody. Sufficient regulatory T cells survive this dual impact of antigen and antibody to emerge as a dominant population that stops residual effectors from rejecting the graft once therapy is withdrawn. (b) Repeated dosing with substantial numbers of marrow cells ensures substantive activation of any antigen-reactive T cells, including precursors of regulatory T cells. Prolonged CD40L antibody therapy ensures that all activated cells will eventually be killed, resulting in tolerance characterized by unregulated deletion.



Herman Waldmann is at the Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, OX1 3RE, UK.  
e-mail: herman.waldmann@pathology.oxford.ac.uk

ments on T cells. The importance of complement fixation was established by showing that graft survival with the same therapeutic protocol was much reduced in mice genetically deficient in C3.

Mice deficient in the Fc receptor- $\gamma$  chain were also unable to maintain long-term grafts, indicating that interaction with Fc receptor-bearing cells is also important. Molar equivalent doses of F(ab')<sub>2</sub>, which lack any Fc function, were ineffective. This latter result should, however, be taken with some caution, as the antibody fragments would be expected to have a much shorter half-life than normal antibodies. Therefore, a role for costimulation blockade under optimal conditions cannot be conclusively ruled out. Finally, Monk *et al.*<sup>4</sup> follow the fate of antigen-specific CD8<sup>+</sup> T cells using tetramer technology, and show that antibodies to CD40L prevent the expansion of CD8<sup>+</sup> T cells, whereas F(ab')<sub>2</sub> fragments do not (albeit with the same caveat relating to antibody half-life).

What are the implications of these findings? At first sight, they would seem to rule out a central role for CD40L antibodies in costimulation blockade. To be sure of this, future studies should examine antibodies that may be more effective in blocking the CD40-CD40L interaction than those used by Monk *et al.* Such antibodies should be tested with engineered Fc regions disabled for effector function.

The thromboembolic episodes observed in early clinical studies with CD40L antibodies<sup>6</sup> have not been fully explained, but could relate to expression of CD40L on

platelets and activated endothelia. On the assumption that Fc-mediated effector mechanisms may be responsible for this adverse effect, the use of antibodies with disabled or incompetent Fc regions seemed like an attractive solution. However, the present findings predict that antibody efficacy will also be lost in such disabled variants.

Recent work<sup>7</sup> suggests that induction of tolerance to transplanted skin by CD40L antibodies is accompanied by the emergence of regulatory CD4<sup>+</sup> T cells. How might these regulatory T cells have been spared from destruction in the Monk study? Perhaps they were less susceptible to lysis, or just unable to express sufficient levels of CD40L during the therapeutic window. They may even resist the synergistic effect of rapamycin.

This seemingly selective sparing of regulatory T cells merits further investigation as a paradigm for creating a favorable balance of regulatory over effector T cells. This is not to say that regulation is always required for tolerance to occur. In animal studies, the use of large doses of donor marrow with extended CD40L antibody treatment has resulted in mixed hematopoietic chimerism<sup>8</sup>. On the basis of past experience with mixed chimerism, this is almost certainly the result of deletion of alloreactive clones. Sufficient and sustained blood-borne antigen, combined with longer-term antibody therapy, will eventually guarantee that all alloreactive T cells, and perhaps even regulatory T cells, are taken out. The nature of the antigen source should influ-

ence the outcome (Fig. 1). If engrafting marrow is the source, then regulatory T cells should be eliminated together with potential effectors; if transplanted tissue is the source, then regulatory T cells should be spared.

It seems that CD40L antibodies can only target and eliminate antigen-activated T cells<sup>4,9,10</sup>. Other tolerance-promoting agents, even those with broad T-cell reactivity, might also do the same by encouraging selective death of antigen-activated T cells through the promotion of apoptosis or the inhibition of survival signals. Identification of targets that best fulfill the goal of selective inactivation of T cells remains a direction for future research.

What is the future for CD40L antibodies in transplantation? The new data will undoubtedly be relevant to the humanized CD40L antibodies already in clinical studies. Consequently, any future use of Fc-competent CD40L antibodies will require an independent strategy for averting the risk of thromboembolism.

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## $\beta$ -receptor polymorphisms: heart failure's crystal ball

David A Kass

**A polymorphism present in about half the general population can predispose to heart failure as well as enhance responsiveness to  $\beta$ -blockers. The mechanism for this is now being revealed (pages 1300–1305).**

Heart failure is typified by a reduced capacity of the heart to provide adequate blood flow and pressure for the body's demands. Drugs that interact with  $\beta$ -adrenergic signaling, such as  $\beta$ -blockers and angiotensin-

pathway inhibitors, are widely prescribed for patients with heart failure and those with diseases such as hypertension that often lead to heart failure. But patient response to such drugs, as well as the propensity of individuals to develop heart failure, is often quite variable. This variance may have potent genetic determinants based on receptor polymorphisms.

One such polymorphism, found in the

$\beta_1$ -receptor, was first identified by Liggett and colleagues<sup>1</sup> and has received a fair amount of recent attention. Individuals homozygous for this potent and very common<sup>2,3</sup> gain-of-function polymorphism at amino acid position 389 (arginine substituted for glycine) show increased heart responsiveness to adrenergic receptor stimulation<sup>4</sup>. These individuals also have enhanced risks of developing hypertension<sup>3</sup> and possibly myocardial infarction<sup>5</sup>.

David A. Kass is at Halsted 500, Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Baltimore, Maryland 21287, USA.  
e-mail: dkass@jhmi.edu